

CAJAL-RETZIUS CELLS AS ELECTROSTATIC GUIDES FOR MIGRATING NEURONS

MICHAEL A. PERSINGER AND N. IAN ROBB

Laurentian University

Summary.—A model is presented to explain one of the possible functions of the Cajal-Retzius cells which are known to mature perinatally but not to survive into late infantile life. In this model the processes of the Cajal-Retzius (C. R.) cells and the ventricular surface act as a transient capacitor-like mechanism during neural migration. Neurons which are connected to the ventricular surface during migration by an end foot are consequently guided by the Cajal-Retzius cell processes located in the upper strata of the cortical molecular layer. Once the end foot is severed migration stops and differentiation begins. When the period of migration nears completion postnatally, the mechanism is destroyed as these cells die or lose their connection with the cortical pial surface. Calculations are given to support the feasibility of this model.

Cajal-Retzius cells comprise a special class of neurons which reach maturity during the perinatal period. They appear during the intrauterine period but atrophy and disappear shortly after birth (Jacobson, 1970). The function of the Cajal-Retzius cells is still not clear. The model reported in this paper indicates that such cells could influence neuronal migration from the ventricular proliferative matrices to the cortex.

Histological Data

Fox and Inman (1966) have reported that Cajal-Retzius cells are bipolar and located in the first layer (molecular) of the neocortex. Two processes that extend parallel to the cortical surface, but in opposite directions from the cell soma, can be identified. Noback and Purpura (1961) identify these processes as dendrites while Duckett and Pearse (1968) have suggested that Cajal-Retzius cells possess a myelinated axon. Duckett and Pearse (1968) observed that sprouts can be seen perpendicular to the main myelinated axon as it maintains its horizontal course in the molecular layer. Some of the sprouts pass down into lamina II of the cortex while others originate in the antiparallel direction and course towards the meningeal layer, in some cases actually penetrating the pial coat. In size, Cajal-Retzius cells may be as large as Betz cells with process lengths of 400 μ . This means the over-all length of the cell may exceed 1 mm (Noback & Purpura, 1961).

The Model

A possible function of Cajal-Retzius cells is shown in Fig. 1. This diagram depicts a capacitor-like situation which may be transiently maintained, during perinatal development, between the processes of these cells (with sprouts

into cortical pial surface) and the pial surface of the (lateral) ventricles. In this situation one of the "plates" is formed by the ventricular pial surface while the other plate is formed by the Cajal-Retzius cells processes (which during this time have cortical pial connections). It can be assumed, for at least initial neuronal-cortical distances, that a number of parallel Cajal-Retzius cell processes (analogous to parallel wires) in a given topographic surface exert an influence that is similar to a parallel plate. In this model an electrical potential exists between the two plates. The young neurons are situated between the two plates of this transient capacitor.

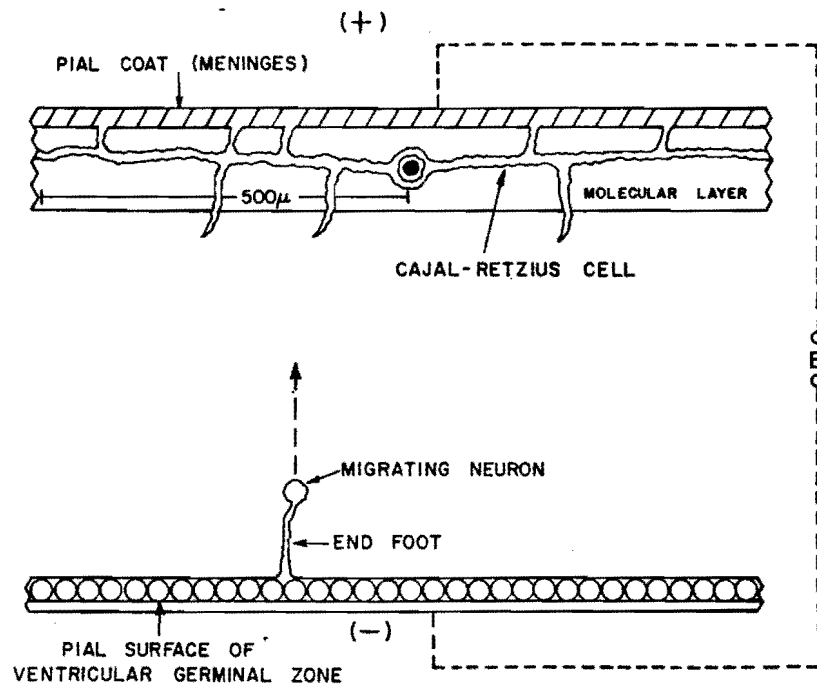


FIG. 1. A model of the possible capacitor-like situation transiently developed between the short-lived Cajal-Retzius cells and the ventricular surface during the period of neuronal migration (not to scale)

When migration from the ventricular germinal zone to the cortex occurs, some young neurons retain a connection to the pial surface by means of an end foot which is not withdrawn until dendritic differentiation has begun (Jacobson, 1970). The function of the end foot is still not clear. In context of this model, the end foot would function as a connector between the neuron and the ventricular plate. Charge on the neuron would be derived from this plate. The neuron, mobile relative to the ventricle, could be pulled slowly toward the other plate (the cells). These cells would then act as an electrostatic-like guide for migrating neurons to the cortex.

Once the neuron had migrated to the appropriate layer, the end foot would be severed, thus ending the connection with the Cajal-Retzius cell-ventricle capacitor mechanism. The limit of the end foot's length may be determined by protoplasmic factors; however, the controlling factors have not been isolated. The main point is that once the end foot is severed, the electrostatic guide mechanism is no longer operative for that neuron and migration halts. Differentiation could then begin.

While existence of the mechanism during perinatal development could facilitate cell migration, the mechanism's operation after the cell has arrived and begins to differentiate would be undesirable. Ectopic cell morphology or layering could develop since it is known that neuronal processes can display dipole configurations which may interact with the mechanism. One could argue in fact that the elliptical shape of many cortical cell soma, with major axes normal to the cortical surface, reflects such early influence upon the first cell processes to emerge. It is known that these processes sprout in the direction of the cortical surface. However, termination of the mechanism occurs shortly after birth or in early infantile life (as migration ends) when the Cajal-Retzius cells die or loosen their attachments from the cortical pial layer and migrate to deeper levels. The transient situation depicted in Fig. 1 then no longer exists.

A topological connection between the neurogenic electrical processes associated with the pial surface of the ventricular region and the Cajal-Retzius cells associated with the pial surface of the cortical region, suggests the possibility of reciprocal influences or feedback. Increased charge on one plate (the ventricular zone) due to cell proliferation could influence the charge characteristics of the other plate (the Cajal-Retzius cells). Whenever sufficient potential (proportional to the number of cells ready for migration) developed between the two plates, triggering of cell migration could take place. The number of cells migrating at any given time would be subject to some threshold value determined by local viscosities, cell charges and overall plate potential differences. As the numbers of cells left the matrix and the relative charge distribution on the plates transiently decreased, triggering frequencies would also decrease. Such a condition would attenuate premature release of neurons and control the number of neurons leaving the proliferative layers at any given time.

Calculations

The time required for a neuron to migrate between plate 1 (the ventricles) and plate 2 (the Cajal-Retzius cells) can be determined in the following manner. It is assumed that the neuron is a sphere with a radius r , density ρ and mass m . The neuron is moving through an aqueous medium of viscosity η with velocity $v(t)$, and electric charge q . Movement occurs under the influence of an electric field E caused by a potential difference over distance D ($E = V/D$). If the viscous friction is taken to be the usual Stokes form, then the equation of motion becomes:

$$m(dv/dt) = qE - 6\pi\eta rv \quad [1]$$

The solution of this differential equation (for zero initial velocity) is:

$$v(t) = M(1 - e^{-at}) \quad [2]$$

where $M = qE/6\pi\eta r$, and $a = 6\pi\eta r/m$.

Integrating the velocity expression, we find:

$$D = Mf(T) \quad [3]$$

where D is the distance travelled in time T , and

$$f(T) = T + (1/a)(e^{-aT} - 1) \quad [4]$$

Using typical data for the brain ($r = 10 \mu$, $\rho = 1 \text{ g/cm}^3$, and $\eta = 7 \times 10^{-3} \text{ g/cm-sec. at } 37^\circ\text{C}$), the value of a is $3.15 \times 10^4 \text{ sec.}^{-1}$. Thus for times greater than 1 millisecond $f(T) = T$.

To proceed, one must estimate the charge q on a neuron. Using the parallel plate capacitor model to represent the pial surface, the charge per unit area on the ventricular pial surface will be $\kappa\epsilon_0 V/D$, where κ is the dielectric constant and ϵ_0 is the permittivity of a vacuum. If the spherical neuron takes a charge proportional to its own area ($4\pi r^2$), the charge would be:

$$q = (4\pi r^2 \kappa \epsilon_0 V)/D \quad [5]$$

and the final equation relating the time T for the neuron to traverse the distance D between the ventricular plate and the Cajal-Retzius cells would be:

$$T = 3\eta D^3 / (2\kappa \epsilon_0 r V^2) \quad [6]$$

Taking $\kappa = 74$, $\epsilon_0 = 8.9 \times 10^{-21} \text{ coul}^2 \text{ sec.}^2/\text{g cm}^3$, $V = v$ millivolts and $D = d$ millimeters, we find:

$$Tv^2/d^3 = 1.8 \times 10^8 \text{ days} \quad [7]$$

For example, if $V = 30 \text{ mV}$ and $D = 1 \text{ mm}$, then $T = 2 \text{ days}$, a result commensurate with experimental values (for the rat). Alternatively, if $V = 17.5 \text{ mV}$, and $D = 1 \text{ mm}$, then $T = 6 \text{ days}$.

Comments

This model is not intended to explain all forms of neuronal migration nor does it demand the inclusion of every cell involved with that process. For one reason, the production of "simple" electrical field patterns would not have the informational capacity to coordinate and maintain this massive phenomenon. Rather, we conceive the present model as an initial guide. As the influenced neurons approach their target areas and the distance from the Cajal-Retzius plates decreases, other guide mechanisms, e.g., chemotropism, with greater specificity, could then take over. We expect the Cajal-Retzius mechanism to influence only a small portion of the cells, which, by their progress through the mi-

grating medium, elicit changes that act as guides to other cells. Even then, the total cell population could not be under the mechanism's control.

The model described in this paper, perhaps unorthodox, is the derivative of a more fundamental conceptual framework that runs contradirectional to homogeneous theories of explanation. In view of the available data and the complex, interwoven processes involved with cell migration, evocation of single theory mechanisms to explain this phenomenon, although heuristically palatable, are naive. It is more likely that a great number of different mechanisms are required during the construction of the brain, the dominance of each being determined by a variety of positional and temporal factors. From this perspective, the conspicuous and unusual cyto-temporal properties of the Cajal-Retzius cells can be interpreted as yet another manifestation of the migrational process.

REFERENCES

- DUCKETT, S., & PEARSE, A. G. E. The cells of Cajal-Retzius in the developing human brain. *J. Anat.*, 1968, 102, 183-187.
- FOX, M. W., & INMAN, O. Persistence of Retzius-Cajal cells in the developing dog brain. *Brain Res.*, 1966, 3, 192-194.
- JACOBSON, M. *Developmental neurobiology*. New York: Holt, Rinehart & Winston, 1970.
- NOBACK, C. R., & PURPURA, D. P. Postnatal ontogenesis of neurons in cat neocortex. *J. comp. Neurol.*, 1961, 117, 291-307.

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